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# THE PATENTS ACT, 1970

Rec'd PCT/PTO 01 OCT 2004

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional specification filed on 05.04.2002 in respect of Patent Application No. 327/MUM/2002 of Cadila Healthcare Limited, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad-380 015, Gujarat, India.

This certificate is issued under the powers vested on me under Section 147 (1) of the Patents Act, 1970.

Dated this 1st day of may 2003

(N. K. GARG)
ASST. CONTROLLER OF PATENTS & DESIGNS

**PRIORITY DOCUMENT**
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

BEST AVAILABLE COPY

# FORM 1

## THE PATENTS ACT, 1970

### APPLICATION FOR GRANT OF PATENT
(See Sections 5(2), 7, 54 and 135 and Rule 33A)

(1) We, **CADILA HEALTHCARE LIMITED,** a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Roads, Ahmedabad 380 015, Gujarat, India

(2) hereby declare –

(a) That we are in possession of an invention titled

**'NEW HETEROCYCLIC COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN MEDICINE'**

(b) That the Provisional Specification relating to this invention is filed with this application;

(c) That there is no lawful ground of objection to the grant of a patent to us.

(3) Further declare that true and first inventor for the said invention is ,

(a) **Mukul R. JAIN,** an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

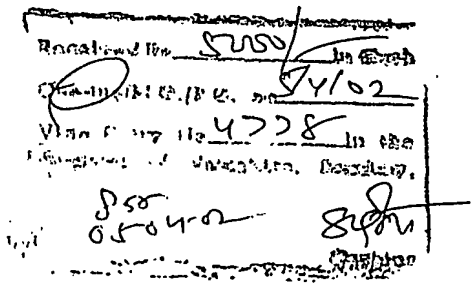
(b) **Gautam D. PATEL,** an Indian citizen, of CADILA HEALTHCARE LIMITED, Zydus towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India

(4) We claim priority from the application(s) filed in the following convention country(ies), particulars of which are as follows: **NIL**

(5) That we are the assignees of the true and first inventors,

(6) That our address for service in India is as follows;

SUBRAMANIAM, NATARAJ & ASSOCIATES
*Attorneys-at-Law*
*Patent and Trademark Attorneys*
E 556, Greater Kailash II,
New Delhi - 110 048, India.
Phone: 91 11 628 5603, 628 6012, 628 6025
Fax: 91 11 628 6005
Email: sna@vsnl.com



(7) Following declaration was given by the inventor

We, **Mukul R JAIN and Gautam D PATEL,** both Indian citizens, of CADILA HEALTHCARE LIMITED, Zydus towers, Satellite Cross Roads, Ahmedabad – 380 015, Gujarat, India,

327/mum/2002

5/4/2002

and the true and first inventors for this invention declare that the applicants herein are our assignees.

Mukul R JAIN

Gautam D PATEL

(8) That to the best of our knowledge, information and belief the facts and matters stated herein are correct and there is no lawful ground of objection to the grant of patent to us on this application.

(9) Following are the attachments with this application:
- (a) Provisional specification in triplicate
- (b) Statement and Undertaking on FORM 3 in duplicate
- (c) Power of Authority
- (d) Form 2 in triplicate
- (e) Power of Authority
- (f) Abstract

Fee Rs. ..... in Cash/Cheque/Bank Draft Bearing No..... dated.....on .....Bank.

We request that a patent be granted to us on any complete specification filed on this application for the said invention.

Dated this 4th day of April , 2002

The Controller of Patents
The Patent Office,
At Mumbai

*for* CADILA HEALTHCARE LIMITED
(name and designation of signatory)

ZRC-MC-004

# FORM 2

The PATENT ACT, 1970
(39 of 1970)

## Provisional Specification

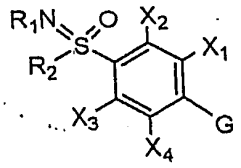
# NEW HETEROCYCLIC COMPOUNDS, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND THEIR USE IN MEDICINE

CADILA HEALTH CARE LTD
Zydus Tower, Satellite Cross Road, Sarkhej-Gandhinagar Highway, Ahmedabad-380015,
Gujarat, India

The following specification describes the nature of the invention and the manner in which it is to be performed:

**Field of Invention**

The present invention relates to novel compounds of general formula (I), their analogs, derivatives, their tautomeric forms, their pharmaceutically acceptable salts and pharmaceutical compositions containing them. The present invention also relates to a process of preparing compounds of general formula (I), their analogs, derivatives, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, and novel intermediates involved in their synthesis.



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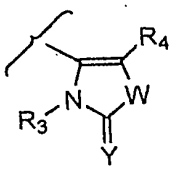

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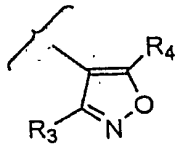

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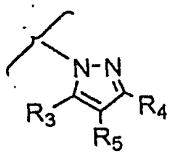

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The compounds of the present invention are useful in the treatment of diseases wherein prostaglandins play a pathophysiological role. Their role have been implicated in a number of diseases which includes rheumatoid arthritis and osteoarthritis, pyrexia, asthma, bone resorption, cardiovascular diseases, dysmenorrhea, premature labour, nephritis, nephrosis, atherosclerosis, hypotension, shock, pain, cancer, and Alzheimer disease.

**Background to the invention**

Inflammation is a disorder which is characterized by redness, fever, swelling and pain. Prostaglandins play a major role in the inflammation process and inhibition of prostaglandin production, especially of $PGG_2$, $PGH_2$ and $PGE_2$ has been a common target to treat inflammation. However, NSAIDs that are commonly used to treat prostaglandin-induced pain and inflammation also effect other prostaglandin-regulated processes not associated with inflammation process. This leads to severe side effects including life threatening gastric ulcers dyspepsia & nephrotoxicity, thereby reducing their therapeutic use.

Previously, NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway, including the enzyme cyclooxygenase (COX). Recently (1991), another isoform of cyclooxygenase enzyme has been discovered which is an inducible form which is now termed as COX-2 enzyme (*PNAS* (1991) 88, 2692-96). COX-1 & COX-2 serve different physiological and pathophysiological functions. COX-1 is the constitutive isoform & is mainly responsible for the synthesis of cytoprotective prostaglandins in the GI tract and for the synthesis of thromboxane, which triggers platelet aggregation in blood platelets. COX-2 is an inducible isoform which is stimulated in response to endotoxins, cytokines, and mitogens. Importantly, COX-2 plays a major role in prostaglandin biosynthesis in inflammatory cells (monocytes/macrophages) and in the central nervous system. (*Current Medicinal Chemistry* (2000) 7, 1041-62). The use of COX-2 as anti-cancer agents is discussed in *Curr Drug Targets* 2001 Mar;2(1):79-106. Hence, the difference in the function of COX-1 & COX-2 provides a goal of separating toxicity from efficacy of NSAIDs by developing drugs that are selective COX-2 inhibitors as anti-inflammatory, analgesic, and/or antipyretic agents with minimization of or without the hematologic liabilities from COX-1 inhibition that plague almost all currently marketed NSAIDs, most of which inhibit both COX-1 & COX-2, with specificity for COX-1 inhibition greatly exceeding that for COX-2 inhibition. Celecoxib and Rofecoxib were the first two selective COX-2 inhibitors approved for selected markets for the treatment of certain inflammatory conditions.

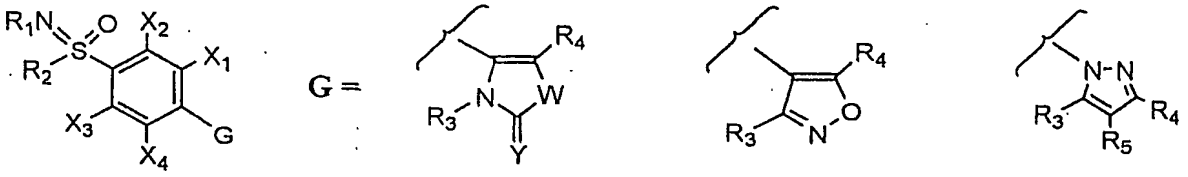
The references below disclose anti-inflammatory compounds that are selective COX-2 inhibitors. Increasing number of publications & patents emerging steadily indicates continuing efforts to find a safe and effective anti-inflammatory agent. Such novel compounds, their methods for preparation are described in EP1006114, EP1099695, EP418845, EP554829, EP0863134, EP0714895, EP0799523, GB2294879, US5474995, US5486534, US5510368, US5686460, US5691374, US5710140, US5723485, US5776967, US5981576, US5922742, US6083969, US6071954, US6071936, US6133292, US6143892, US6274590, WO9415932, WO9427980, WO9500501, WO9515315, WO9515316, WO9515317, WO9515318, WO9518799, WO9603387, WO9603392, WO9606840, WO9609304, WO9610012, WO9616934, WO9619469, WO9621667, WO9623786, WO9624585, WO9625405, WO9631509, WO9636623, WO9637467, WO9638418,

WO9636617, WO9703667, WO9703953, WO9713755, WO9714691, WO9716435, WO9727181, WO9734882, WO9737984, WO9746524, WO97727181, WO9804527, WO9807425, WO9807714, WO9811080 WO9813483, WO9816227, WO9821195, WO9822442, WO9825896, WO9841511, WO9841516, WO9843966, WO9852940, WO9910331, WO9910332, WO9912930, WO9915503, WO9923087, WO9935130, WO0026216, WO0052008, WO0024719, WO0134577, WO0140216.

Tumor necrosis factor α (TNF-α) is described as a key proinflammatory mediator in autoimmune diseases. This 26 kDa enzyme is membrane associated until processed into a smaller (17 kDa) soluble form by TNF-α converting enzyme (TACE). The compounds of the present invention are also useful in the treatment of inflammatory diseases such as arthritis by inhibiting TNF-α, or TACE or by inbiting the production of Tumor necrosis factor- α.

**Summary of the invention**

The present invention describes a group of novel compounds useful in the treatment of inflammatory diseases, cytokine related, specially, TNF-α mediated diseases, cyclooxygenase related diseases, more particularly COX-2 and other related disorders like inflammation and pain. The novel compounds are defined by the general formula (I) below:




(I) A B C

The compounds of the present invention are useful in the treatment of the human or animal body, in particular for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention of colorectal cancer. They are also useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhoea, headache, toothache, sprains and strains, myostis, neuralgia, synovitis, bursitis, tendinitis, injuries following surgical and dental procedures,

post-operative inflammation including ophthalmic surgery such as cataract and refractive surgery, menstrual cramps, premature labor, These compounds may also be used in the treatment of arthritis, such as rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, skin inflammation disorders such as psoriasis, eczema, burning and dermatitis with better efficacy, pbtency and minimum toxic effects.

The main objective of the present invention thus is to provide novel compounds of general formula (I), their analogs, derivatives, their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, their polymorphs and pharmaceutical compositions containing them or their mixtures.

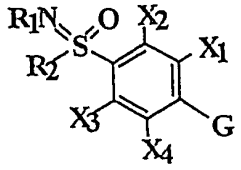
Another objective of the present invention is to provide a process for the preparation of novel compounds of general formula (I), their analogs, derivatives, their tautomeric forms, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, their polymorphs and pharmaceutical compositions containing them.

The present invention also aims at providing pharmaceutical compositions containing compounds of general formula (I), their analogs, derivatives, their tautomeric forms, their pharmaceutically acceptable salts, solvates, and their mixtures having pharmaceutically acceptable carriers, solvents, diluents and other media normally employed in their manufacture.

The compounds of the present invention provides a method of treatment of cyclooxygenase mediated diseases, by administering a therapeutically effective & non-toxic amount of the compound of formula (I) or their pharmaceutically acceptable compositions to the mammals.

**Detailed Description of the description**

The novel compounds of the present invention are defined by the general formula (I) below:



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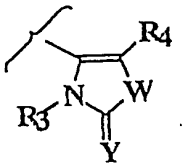

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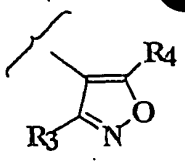

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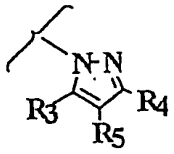

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Where $R_1$ represents hydrogen, substituted or unsubstituted groups selected from alkyl, aralkyl, acyl, alkylsulfonyl, arylsulfonyl groups; $R_2$ represents alkyl or NHR where R represents hydrogen, lower alkyl, $-NH_2$, alkylamino, acylamino, aralkylamino group;

$X_1$, $X_2$, $X_3$, $X_4$ may be same or different and represent

hydrogen,

cyano, nitro,

halo,

carboxyl, formyl,

hydrazino, azido,

amino, thio, hydroxy,

or substituted or unsubstituted groups selected from

alkyl which may be linear or branched, alkenyl,

oximealkyl,

alkoxy, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thioalkyl, carboxyalkyl, haloalkyl, aminoalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkoxycarbonylalkyl

hydrazinoalkyl, alkylhydrazido,

acyl,

aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, aralkoxyalkyl, aralkenyl,

amidino, carboxamidoalkyl, acylamino,

cyanoamidino, cyanoalkyl,

N-aminocarbonylalkyl, N-arylaminocarbonyl, N-alkylaminocarbonyl, N,N-dialkylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, N-alkyl-N-hydroxyaminocarbonyl, N-alkyl-N-hydroxyaminocarbonylalkyl, carboxyalkylaminocarboxy, N-alkylamino, N,N-dialkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, N-aralkyl-N-alkylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, N-aralkyl-N-alkylaminoalkyl,

arylthio, aralkylthio, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, aminesulfonyl, sulfonamidyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonylalkyl, cycloalkyl, cycloalkenyl, heterocyclic, heteroaryl, heterocyclicalkyl, sulfamyl groups; two adjacent groups may form a methylenedioxy or a ethylenedioxy group;

$R_3$ is selected from substituted or unsubstituted aryl or heterocyclic groups; $R_4$ and $R_5$ is selected from hydrogen atom, halogen atom, substituted or unsubstituted groups selected from linear or branched alkyl groups.

Suitable substituents on $R_3$ may be selected from cyano, nitro, halo, carboxyl, hydrazino, azido, formyl, amino, thio, hydroxy or substituted or unsubstituted groups selected from alkyl which may be linear or branched, alkoxy, hydrazinoalkyl, alkylhydrazido, acyl, carboxyalkyl, haloalkyl, aminoalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, aralkoxyalkyl, alkoxycarbonylalkyl, amidino, carboxamidoalkyl acylamino, cyanoamidino, cyanoalkyl, N-aminocarbonylalkyl, N-arylaminocarbonyl, carboxyalkylaminocarboxy, N-alkylamino, N,N-dialkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, arylthio, aralkylthio, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, alkoxycarbonyl, aminocarbonyl, cycloalkyl, heterocyclic, heterocyclicalkyl, aralkyl, sulfamyl groups; two adjacent groups may form a methylenedioxy or a ethylenedioxy group;

Suitable substituents on $X_1$, $X_2$, $X_3$, $X_4$ may be selected from cyano, nitro, halo, carboxyl, hydrazino, azido, formyl, amino, thio, hydroxy or substituted or unsubstituted groups selected from alkyl which may be linear or branched, alkoxy, hydrazinoalkyl, alkylhydrazido, acyl, carboxyalkyl, haloalkyl, aminoalkyl, haloalkoxy, hydroxyalkyl, alkoxyalkyl, thioalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, aralkoxyalkyl, alkoxycarbonylalkyl, amidino, carboxamidoalkyl acylamino, cyanoamidino, cyanoalkyl, N-aminocarbonylalkyl, N-arylaminocarbonyl, carboxyalkylaminocarboxy, N-alkylamino, N,N-dialkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-



dial

alkyl-N-arylamino, N-alkylaminoalkyl, N,N-dialkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, arylthio, aralkylthio, N-alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N,N-dialkylaminosulfonyl, N-alkyl-N-arylaminosulfonyl, alkoxycarbonyl, aminocarbonyl, cycloalkyl, heterocyclic, heterocyclicalkyl, aralkyl, sulfamyl groups.

Where the term "alkyl" is used anywhere in the specification, either alone or within other terms such as "haloalkyl", "hydroxyalkyl", " alkylthio", "alkylsulfonyl" etc. it includes linear or branched radicals having one to ten carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to six carbon atoms. Examples of such radicals include but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, isohexyl, heptyl, octyl etc. The term "alkenyl" includes linear or branched radicals having at least one carbon-carbon double bond of two to ten carbon atoms or, preferably, two to six carbon atoms. Examples of such radicals include ethenyl, n-propenyl, butenyl, and the like. The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms. The term "haloalkyl" includes radicals wherein any one or more of the alkyl carbon atoms is substituted with halogen atoms as defined above. Examples include monohaloalkyl, dihaloalkyl, polyhaloalkyl and similar radicals. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. The alkyl group in haloalkyl group is a lower alkyl group and is termed lower haloalkyl group. "Lower haloalkyl" includes radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trichloroethyl, pentafluoroethyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, and the likes. The term "hydroxyalkyl" includes linear or branched alkyl radicals having one to ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals. More preferred hydroxyalkyl radicals are "lower hydroxyalkyl" radicals having one to six carbon atoms and one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, and hydroxyhexyl.

The terms "alkoxy" and "alkoxyalkyl" includes linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. Preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. The term "alkoxyalkyl" also includes alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. Preferred alkoxyalkyl radicals are "lower alkoxyalkyl" radicals having one to six carbon atoms and one or two alkoxy radicals. Examples of such radicals include methoxymethyl, methoxyethyl, ethoxyethyl, methoxybutyl, methoxypropyl and the like. The "alkoxy" or "alkoxyalkyl" radicals may further contain substitution consisting of one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, trifluoroethoxy, fluoroethoxy and the like.

The term "aryl", alone or in combination, includes carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl. The term "heterocyclic" includes saturated, partially saturated and unsaturated ring-shaped radicals, the heteroatoms selected from either nitrogen, sulfur and oxygen. Examples of saturated heterocyclic radicals include saturated 3 to 7-membered heteromonocyclic group containing one or more heteroatoms selected from N, O and S. Examples of such groups include but not limited to aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxazepinyl, thiazepinyl, oxazolidinyl, thiazolidinyl and the like; examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole and the like; the term "heteroaryl" includes unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic group containing one or more heteroatoms selected from O, N, S. Example of such groups include but not limited to pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl. pyridazinyl, triazolyl, (e.g., 1H-1,2,4-triazolyl, 1H-1,2,3-tetrazolyl etc.),

indolyl, isoindolyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl, pyranyl, 2-furyl, 3-furyl, benzoxazolyl, benzoxadiazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, benzothiadiazolyl and the like. The term also includes radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The aforesaid "heterocyclic group" may have 1 to 4 substituents such as lower alkyl, haloalkyl, dihaloalkyl, trihaloalkyl, hydroxy, oxo, amino and lower alkylamino, lower alkoxy, halo, lower thioalkyl, acyl, acylamino groups. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals and more preferably examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, pyrazinyl, pthalazinyl, quinazolinyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzothiazolyl, and the like.

The term "sulfonyl", used alone or in combination with other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl" includes alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. More preferred alkylsulfonyl radicals are lower alkylsulfonyl radicals having one to six carbon atoms. Examples of such lower alkylsulfonyl radicals include methylsulfonyl, ethylsulfonyl and propylsulfonyl. The term "arylsulfonyl" includes aryl radicals as defined above, attached to a sulfonyl radical. Examples of such radicals include phenylsulfonyl. The terms "sulfamyl," "aminosulfonyl" and "sulfonamidyl," whether alone or used with terms such as "N-alkylaminosulfonyl" and "N-arylaminosulfonyl", "N,N-dialkylaminosulfonyl", "N-alkyl-N-arylaminosulfonyl", denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2NH_2$). The terms "N-arylaminosulfonyl" and "N,N-dialkylaminosulfonyl" denote sulfamyl radicals substituted, respectively with one alkyl radical, or two alkyl radicals. More preferred alkylaminosulfonyl radicals are "lower alkylaminosulfonyl" radicals having one to six carbon atoms. Examples of such lower alkylaminosulfonyl radicals include N-methylaminosulfonyl, N-ethylaminosulfonyl, N-methyl-N-ethylaminosulfonyl and the like. The terms "N-arylaminosulfonyl" and "N-alkyl-N-arylaminosulfonyl" denote sulfamyl radicals substituted respectively with one aryl radical or one alkyl and one aryl radical. Preferred N-alkyl-N-arylaminosulfonyl radicals are lower N-alkyl-N-arylsulfonyl radicals

having alkyl radicals of one to six carbon atoms. Examples of such lower N-alkyl-N-arylsulfonyl radicals are N-ethyl-phenylaminosulfonyl and the like.

The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -$CO_2H$. The terms "alkanoyl" or "acyl" include radicals derived from carboxylic acids and include but not limited to substituted or unsubstituted groups selected from formyl, acetyl, propionyl (propanoyl), butanoyl (butyryl), isobutanoyl (isobutyryl), valeryl (pentanoyl), isovaleryl, pivaloyl, hexanoyl, benzoyl or the like. The term "carbonyl" used either alone or with other terms, such as "alkylcarbonyl", denotes - (C=O)-. The term "alkylcarbonyl" includes radicals having a carbonyl radical substituted with an alkyl radical such as acyl or alkanoyl described above. The term "alkylcarbonylalkyl" denotes an alkyl radical substituted with an "alkylcarbonyl" radical. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl radical. Preferably, "lower alkoxycarbonyl" includes alkoxy radicals having one to six carbon atoms. Examples of such "lower alkoxycarbonyl" ester radicals include substituted or unsubstituted methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl and hexyloxycarbonyl. The term "alkoxycarbonylalkyl" includes radicals having "alkoxycarbonyl", as defined above substituted to an alkyl radical. Preferred alkoxycarbonylalkyl radicals are "lower alkoxycarbonylalkyl" having lower alkoxycarbonyl radicals as defined above attached to one to six carbon atoms for example methoxycarbonylmethyl, tert-butoxycarbonylethyl, and methoxycarbonylethyl. The term "aminocarbonyl" when used separately or with other terms such as "aminocarbonylalkyl", "N-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl" and "N-alkyl-N-hydroxyaminocarbonylalkyl", substituted or unsubstituted. The terms "N-alkylaminocarbonyl" and "N,N-dialkylaminocarbonyl" denote aminocarbonyl radicals which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote aminocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals.

The term "amidino" denotes an -C(=NH)-$NH_2$ radical. The term "cyanoamidino" denotes an -C(=N-CN)-$NH_2$ radical. The term "heterocyclicalkyl" includes heterocyclic-substituted alkyl radicals. More preferred heterocyclicalkyl radicals are "lower heterocyclicalkyl" radicals having one to six carbon atoms and a heterocyclic radical. Examples include such radicals as pyrrolidinylmethyl, pyridylmethyl and thienylmethyl. The term "aralkyl" includes aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, diphenylethyl and the like. The aryl in said aralkyl may be additionally substituted with halo, alkyl, alkoxy, haloalkyl, haloalkoxy, hydroxy, amino, acylamino, alkoxycarbonyl, alkylthio and the like. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" includes radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. The term "cycloalkenyl" includes unsaturated cyclic radicals having three to ten carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and the like. The term "alkylthio" includes radicals containing a linear or branched alkyl radical attached to a divalent sulfur atom. Example of alkylthio are methylthio ($CH_3$-S-), ethylthio, butylthio, and the like. The term "alkylsulfinyl" includes radicals containing a linear or branched alkyl radical attached to a divalent-S(=O)-atom.

The term "aminoalkyl" includes alkyl radicals substituted with amino radicals. Preferred aminoalkyl radicals are "lower aminoalkyl" having one to six carbon atoms. Examples include aminomethyl, aminoethyl and aminobutyl. The term "alkylaminoalkyl" includes aminoalkyl radicals having the nitrogen atom substituted with at least one alkyl radical. Preferred alkylaminoalkyl radicals are "lower alkylaminoalkyl" having one to six carbon atoms attached to a lower aminoalkyl radical as described above. The terms "N-alkylamino" and "N-N-dialkylamino" denote amino groups which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred alkylamino radicals are "lower alkylamino" radicals having one or two alkyl radicals of one to six carbon atoms, attached to a nitrogen atom. Suitable "alkylamino" may be N,N-dimethylamino, N,N-diethylamino or the

like. The term "arylamino" denotes amino groups which have been substituted with one or two aryl radicals, such as N-phenylamino. The "arylamino" radicals may be further substituted on the aryl ring portion of the radical. The term "aralkylamino" denotes amino groups which have been substituted with one or two aralkyl radicals, such N-benzylamino. The "aralkylamino" radicals may be further substituted on the aryl ring portion of the radical. The terms "N-alkyl-N-arylamino" and "N-aralkyl-N-alkylamino" denote amino groups which have been substituted with one aralkyl and one alkyl radical, or one aryl and one alkyl radical; respectively, to an amino group. The terms "N-arylaminoalkyl" and "N-aralkylaminoalkyl" denote amino groups which have been substituted with one aryl radical or one aralkyl radical, respectively, and having the amino group attached to an alkyl radical. Preferred arylaminoalkyl radicals are "lower arylaminoalkyl" having the arylamino radical attached to one to six carbon atoms. Examples of such radicals include N-phenylaminomethyl and N-phenyl-N-methylaminomethyl. The terms "N-alkyl-N-arylaminoalkyl" and "N-aralkyl-N-alkylaminoalkyl" denotes N-alkyl-N-arylamino and N-alkyl-N-aralkylamino groups, respectively, and having the amino group attached to alkyl radicals. The term "acyl", whether used alone, or with another term such as "acylamino" denotes a radical provided by the residue after removal of hydroxyl from an organic acid. The term "acylamino" includes an amino radical substituted with an acyl group. Examples of an "acylamino" radical is acetylamino or acetamido ($CH_3C(=O)$-NH-) where the amine may be further substituted with alkyl, aryl, or aralkyl. The term "arylthio" includes aryl radicals of six to ten carbon atoms, attached to a divalent sulfur atom. An example of "arylthio" is phenylthio. The term "aralkylthio" includes aralkyl radicals as described above, attached to a divalent sulfur atom. An example of "aralkylthio" is benzylthio. The term "aryloxy" includes aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy. The term "aralkoxy" includes oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. Preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. The term "haloaralkyl" includes aryl radicals as defined above "carboxyhaloalkyl" includes carboxyalkyl radicals as defined above having halo radicals attached to the alkyl portion. The term "aralkenyl" includes aryl radicals attached to alkenyl radicals having two to en carbon atoms, such as phenylbutenyl, and phenylethenyl or styryl.

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

The compounds of general formula (IA) may be prepared by one or more routes or combinations of reactions outlined in schemes 1 and 2 outlined below which comprises:

**Scheme I**

a) i) Reacting a carbamate of the formula II, wherein $R_2$,$R_3$,$R_4$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with acetic acid to yield a compound of general formula III wherein all the symbols are as defined earlier;

ii) Reacting the compound of formula III wherein all the symbols are as defined earlier with an oxidizing compound such as $H_2O_2$, peracids and such other oxidizing agents to yield a sulfoxide of formula V wherein all the symbols are as defined earlier;

iii) Reacting the sulfoxide of formula V wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoxamine of formula (IAa), wherein all the symbols are as defined in formula (IA) and $R_1$= H;

iv) optionally, compound of formula (IAa) is converted to compound of formula (IA) by suitable agents to get appropriate $R_1$ group. Alternatively, the compound of formula V may be converted to compound (IA) by treating with appropriate agents;

v) optionally, if desired, the compound of formula (IAa) or (IA) are converted to pharmaceutically acceptable salts;

b) i) Reacting a carbamate of formula II, wherein, $R_2$, $R_3$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with an oxidizing compound such as $H_2O_2$, peracids and such other

oxidizing agents, to yield a sulfoxide of formula IV wherein all the symbols are as defined earlier;

ii) Reacting the sulfoxide of formula IV wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoxamine of formula VI, wherein all the symbols are as defined in formula (IA) and $R_1$= H;

iii) Reacting the carbamate of formula VI wherein $R_2$, $R_3$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with acetic acid to yield compounds of formula (IAa) where all the symbols are as defined earlier;

iv) Optionally compound of formula (IAa) is converted to compound of formula (IA) by suitable agents to get suitable R groups;

v) optionally, if desired, the compound of formula (IAa) or (IA) are converted to pharmaceutically acceptable salts;

c) i) Reacting a carbamate of formula II, wherein, $R_2$, $R_3$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with an oxidizing compound such as $H_2O_2$, peracids and such other oxidizing agents, to yield a sulfoxide of formula IV, wherein all the symbols are as defined earlier;

ii) Reacting the sulfoxide of formula IV wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoxamine of formula VI, wherein all the symbols are as defined in formula (IA) and $R_1$= H;

iii) The carbamate of formula VI is converted to compound of formula VII by suitable agents to get appropriate $R_1$ group. Alternatively, the compound of formula IV may be converted to compound VII by treating with appropriate agents;

iv) Reacting the compound of formula VII wherein $R_2$, $R_3$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with acetic acid to yield compounds of formula (IA) where all the symbols are as defined earlier;

v) optionally, if desired, the compound of formula (IA) are converted to pharmaceutically acceptable salts;

d) i) Reacting a carbamate of formula II, wherein, $R_2$, $R_3$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with an oxidizing compound such as $H_2O_2$, peracids and such other oxidizing agents, to yield a sulfoxide of formula IV wherein all the symbols are as defined earlier;

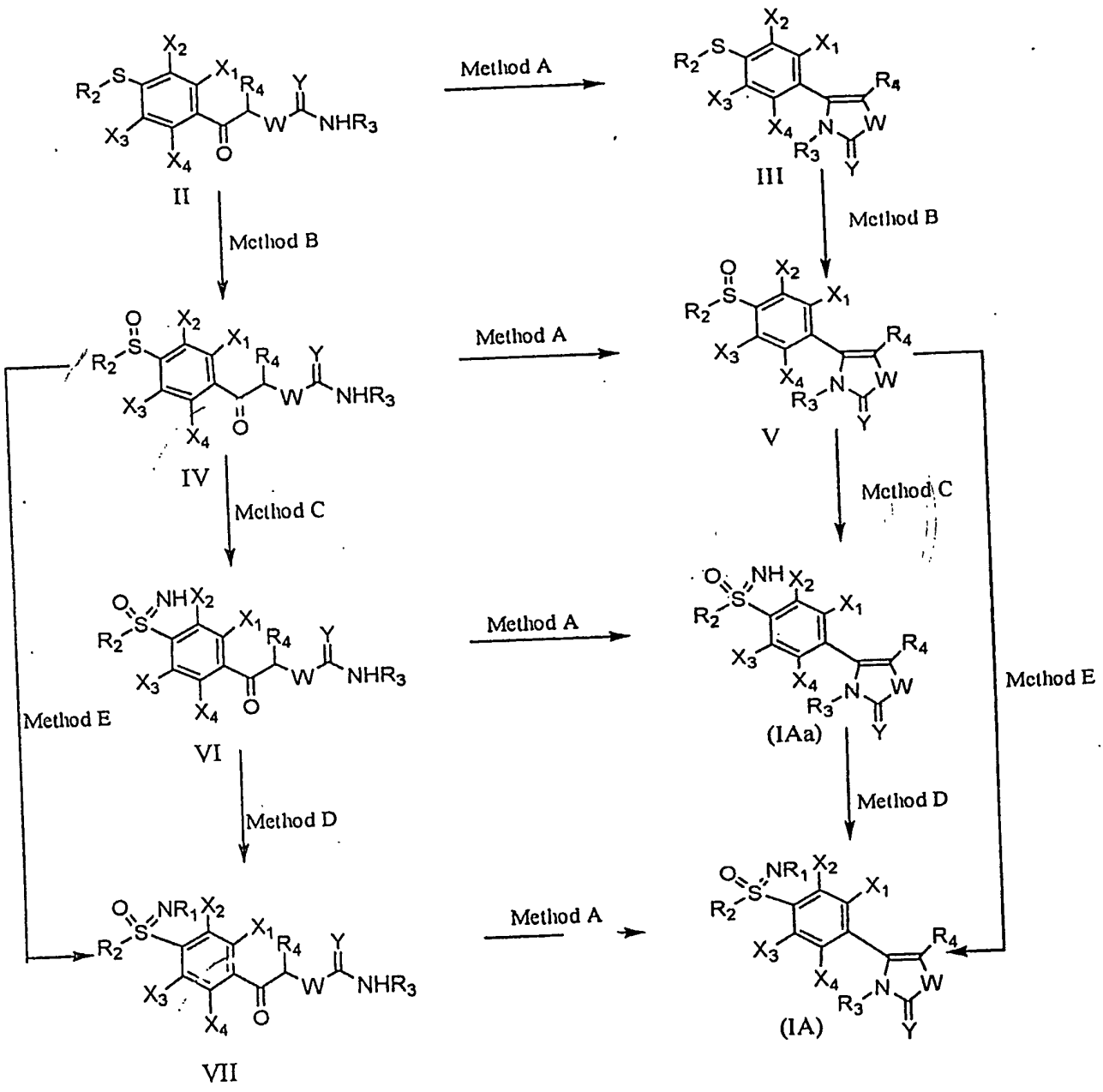
ii) Reacting the carbamate of the formula IV, wherein $R_2$, $R_3$, $X_1$, $X_2$, $X_3$, $X_4$, W, Y are as defined earlier, with acetic acid to yield a compound of general formula V wherein all the symbols are as defined earlier;

iii) Reacting the sulfoxide of formula V wherein all the symbols are as defined earlier with an appropriate iminating agents such as $HN_3$, o-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoximine of formula (IAa), wherein all the symbols are as defined in formula (IA) and $R_1$= H;

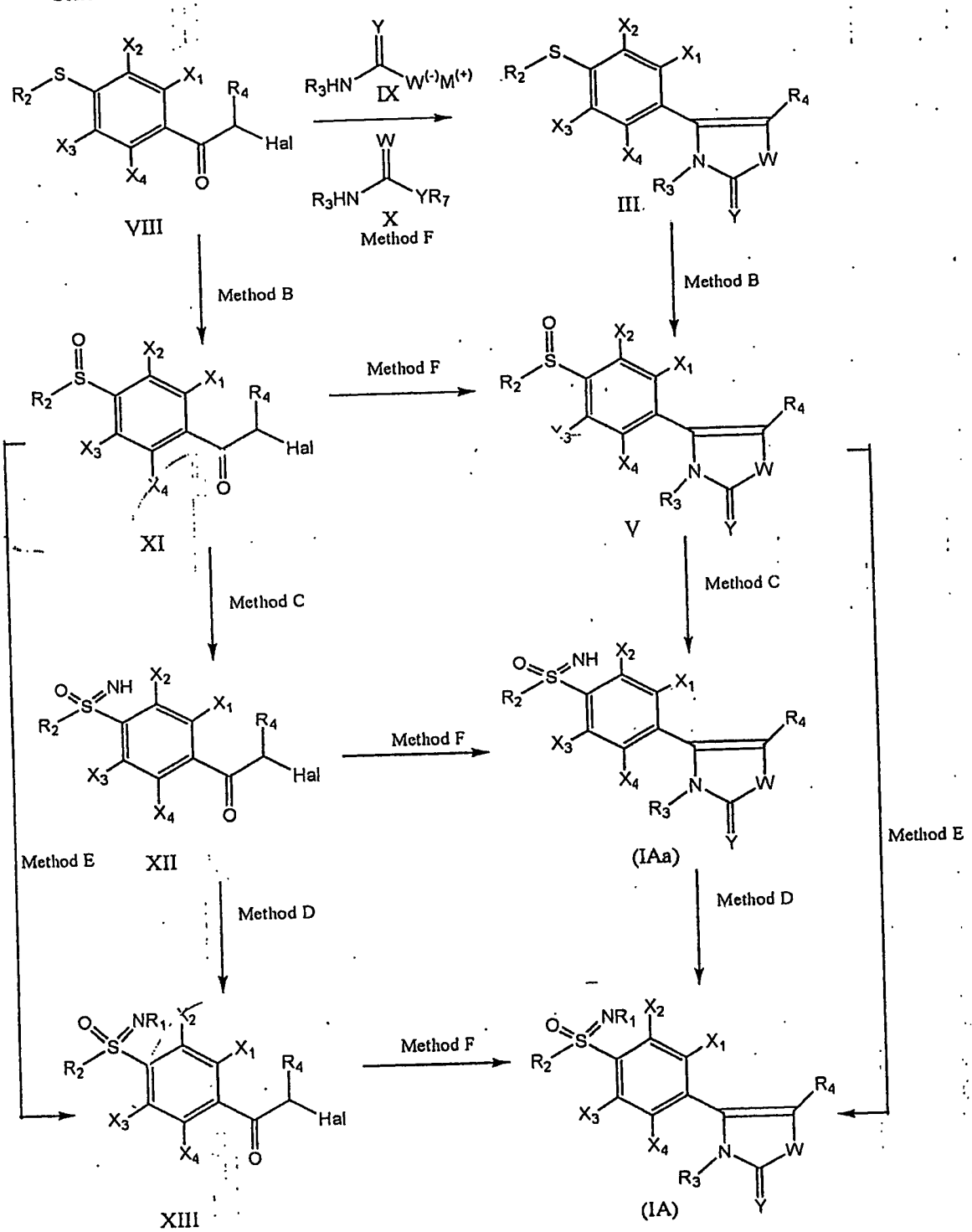
iv) optionally, compound of formula (IAa) is converted to compound of formula (IA) by suitable agents to get appropriate $R_1$ group. Alternatively, the compound of formula V may be converted to compound (IA) by treating with appropriate agents;

v) optionally, if desired, the compound of formula (IAa) or (IA) are converted to pharmaceutically acceptable salts;

Scheme-1


Method A
II
III
Method B
IV
V
Method C
VI
(IAa)
Method D
VII
(IA)
Method E

Scheme- 2


VIII
IX
X
Method F
III.
Method B
Method B
XI
Method F
V
Method C
Method C
XII
Method F
(IAa)
Method E
Method E
Method D
Method D
XIII
Method F
(IA)

Scheme II

e) i) Reacting a compound of formula VIII wherein, $R_2$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$ are as defined earlier and Hal represents a halogen atom such as chlorine, bromine or iodine atom with an aryl dithiocarbamate salt IX where all the symbols are as defined earlier and M represents an alkali metal atom such as Na, K and the like or alkaline earth metal atom such as lithium, magnesium and the like or with a compound of formula X where all the symbols are as defined earlier, and $R_7$ represents lower alkyl group such as methyl, ethyl, propyl and the like, to yield a compound of formula III after dehydration of the intermediate compound XIV formed;

ii) Reacting the compound of formula III wherein all the symbols are as defined earlier with an oxidizing compound such as $H_2O_2$, peracids and such other oxidizing agents to yield a sulfoxide of formula V wherein all the symbols are as defined earlier;

iii) Reacting the sulfoxide of formula V wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoxamine of formula (IAa), wherein all the symbols are as defined in formula (IA) and $R_1$= H;

iv) optionally, compound of formula (IAa) is converted to compound of formula (IA) by suitable agents to get appropriate $R_1$ group. Alternatively, the compound of formula V may be converted to compound (IA) by treating with appropriate agents;

v) optionally, if desired, the compound of formula (IAa) or (IA) are converted to pharmaceutically acceptable salts;

f) i) Reacting compound of formula VIII wherein $R_2$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$ are as defined earlier and Hal represents a halogen atom such as chlorine, bromine or iodine atom with an oxidizing compound such as $H_2O_2$, peracid and such other oxidizing agents to yield a compound of formula XI wherein all the symbols are as defined earlier;

ii) Reacting the sulfoxide of formula XI wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoxamine of formula XII, wherein all the symbols are as earlier;

iii) Reacting the sulfoxamine of formula XII with compound of formula IX where all the symbols are as defined earlier amd M represents an alkali metal atom such as Na, K and the like or alkaline earth metal atom such as lithium, magnesium and the like or with a compound of formula X where all the symbols are as defined earlier, and $R_7$ represents lower alkyl group such as methyl, ethyl, propyl and the like, to yield compound of formula (IAa) which is compound of formula (IA) where all the symbols are as defined earlier and $R_1$=H;

iv) optionally, compound of formula (IAa) is converted to compound of formula (IA) by suitable agents to get appropriate $R_1$ group;

v) optionally, if desired, the compound of formula (IAa) or (IA) are converted to pharmaceutically acceptable salts;

g) i) Reacting compound of formula VIII wherein $R_2$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, are as defined earlier and Hal represents a halogen atom such as chlorine, bromine or iodine atom with an oxidizing compound such as $H_2O_2$, peracid and such other oxidizing agents to give compound of formula XI wherein all the symbols are as defined earlier;

ii) Reacting the sulfoxide of formula XI wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoximine of formula XII, wherein all the symbols are as earlier;

iii) Reacting a compound of formula XII with suitable reagents to get a compound of formula of formula XIII, where all the symbols are as defined earlier. Alternatively,

the compound of formula XI may be converted to compound XIII by treating with appropriate agents;

iv) Reacting the compound of formula XIII wherein $R_2$, $R_3$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, are as defined earlier, with compound of formula IX where all the symbols are as defined earlier and M represents an alkali metal atom such as Na, K and the like or alkaline earth metal atom such as lithium, magnesium and the like or with a compound of formula X where all the symbols are as defined earlier, and $R_7$ represents lower alkyl group such as methyl, ethyl, propyl and the like, to yield a compound of formula (IA).

v) optionally, if desired, the compound of formula (IA) is converted to pharmaceutically acceptable salts;

h) i) Reacting compound of formula VIII wherein $R_2$, $R_4$, $X_1$, $X_2$, $X_3$, $X_4$, are as defined earlier and Hal represents a halogen atom such as chlorine, bromine or iodine atom with an oxidizing compound such as $H_2O_2$, peracid and such other oxidizing agents to give compound of formula XI wherein all the symbols are as defined earlier;

ii) Reacting a compound of formula XI with aryl dithiocarbamate salt IX where all the symbols are as defined earlier and M represents an alkali metal atom such as Na, K and the like or alkaline earth metal atom such as lithium, magnesium and the like or with a compound of formula X where all the symbols are as defined earlier, and $R_7$ represents lower alkyl group such as methyl, ethyl, propyl and the like, to yield a compound of formula V after dehydration of the intermediate compound of formula XIV formed;

iii) Reacting the sulfoxide of formula V wherein all the symbols are as defined earlier with an appropriate iminating agent such as $HN_3$, O-substituted hydroxylamines such as O-mesitylenesulfonyl hydroxylamine (MSH) and the like to yield sulfoxamine of formula (IAa), wherein all the symbols are as defined in formula (I) and $R_1$= H;

iv) optionally, compound of formula (IAa) is converted to compound of formula (IA) by suitable agents to get appropriate $R_1$ group. Alternatively, the compound of formula V may be converted to compound (IA) by treating with appropriate agents;

v) optionally, if desired, the compound of formula (IAa) or (IA) are converted to pharmaceutically acceptable salts;

The reactions described in the processes (a) to (h) outlined above may be performed by using the methods described herein:

Method A:

The carbamates of formula II, IV, VI or VII may be converted to compounds of formula III, V, (IAa) or (IA) respectively by reacting the respective carbamates with acids, more preferably organic acids such as acetic acid, propionic acid and the like. Temperature in the range of ambient to reflux temperature of the solvent may be used. The acid may be used as the solvent. Solvents such as toluene, xylene, DMF, DMSO, dioxane, THF, di-isopropyl ether, *tert* butyl methyl ether may be used as co-solvent. Preferably, acetic acid at reflux temperature is used. Anhydrous acetic acid is more preferred. Reaction time may range from 1-24 hours, preferably 6-20 hours, depending on the substrate as evident from the process controls.

Method B:

The mercapto compounds of formula II, III, or VIII may be converted to the respective sulfoxides by reacting with an oxidizing agent. Suitable oxidizing agents may be selected from but not limited to peroxides and peroxyacids and their salts. Suitable oxidizing agents is selected from $H_2O_2$, meta-peroxides of Na, K, and the like, oxone®, sodium perborate, sodium tungstate and the like, peracetic acid, m-chloroperbenzoic acid, magnesium monoperoxyphthalate, and the like. Suitable solvents are based on the oxidizing agents used and are selected from water, acetic acid, acetonitrile, dichloromethane, acetone, THF, methanol, ethanol and the like or a mixture thereof. Reaction temperature may range from –78 °C to 40 °C, based on the solvent used.

Method C:

The sulfoxide compounds of formula IV, V or XI may be converted to sulfoximine compounds by reacting with suitable iminating agents such as hydrazoic acid ($HN_3$) which may be generated by the reaction of $NaN_3$ with conc. sulfuric acid in solvents such as $CH_2Cl_2$, $CHCl_3$ and the like. Temperature in the range –10 °C to ambient temperature may be used. Alternatively, sulfoxides of formula IV or V may be treated with O-substituted hydroxylamines, such as O-mesitylenesulfonylhydroxylamine (MSH), followed by a base such as KOH, NaOH, $NaHCO_3$ and the like. Solvents such as $CH_2Cl_2$, $CHCl_3$ may be used.

Method D:

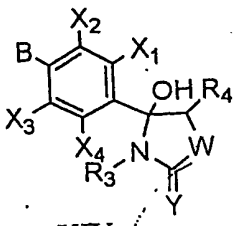
The sulfoximines of formula VI, Iaa or XII may be converted to corresponding alkylated compounds by reaction with appropriate alkylating/ acylating agents in the presence of a base. The alkylating/acylation agent depends on the desired group $R_1$ such as suitably substituted alkyl halides/acylhalides or acyl anhydrides. When $R_1$=Me, formic acid/formaldehyde mixture is used. Solvents used may be DMF, DMSO, acetone, THF, diaoxane, toluene, xylene and the like or a mixture thereof. Bases such as $K_2CO_3$, $Na_2CO_3$, NaH, KI, nBuLi, or a mixture thereof may be used. Reaction temperature may range from 0 °C to reflux temperature of the solvent(s) used.

Method E:

The sulfoxide compounds may be directly converted to substituted sulfoximes compounds by reacting with suitable reagents; such as Tosylazide, Chloramine T, in solvents such as ethanol, methanol and the like, followed by basification to yield $R_1$= Tosyl groups. Alternatively, reaction with arylamines in the presence of t-BuOCl gives N-arylsulfoximines.

Method F:

The haloketones of formula VIII, XI, XII or XIII may be converted to corresponding cyclic compounds of formula III, V, (IAa) or ( IA) respectively by reacting with either a compound of formula IX or with a compound of formula X under suitable conditions through an initial formation of a compound of formula (XIV),

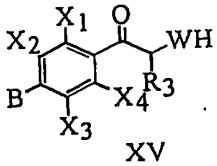


XIV

where B represents the radicals $-SR_2$, $-SOR_2$, $S(O)(NH)R_2$, $S(O)(NR_1)R_2$ respectively and all other symbols are as defined earlier. The compound of formula (XIV) may be obtained by the reaction of compound of formula IX or X with haloketone of formula VIII, XI, XII or XIII in a solvent such as an alcohol like methanol, ethanol, isopropanol, and the like; acetone, THF, dioxane, acetonitrile, toluene, xylene and the like or a mixture thereof. Reaction temperature may range from ambient to reflux temperature of the solvent(s) used. The compounds of formula XIV is converted to respective compound of formula III, V, (IAa) or (IA) by dehydration by refluxing in a suitable medium such as an aqueous alcoholic medium containing a mineral acid such as HCl or $H_2SO_4$, or $H_3PO_4$; organic acids such as PTSA may also be used in an organic solvent such as toluene, xylene and the like; organic acid such as acetic acid, propionic acid or trifluoroacetic acid may also be used.

It is preferred to use compounds of formula IX, when Y is S and W=S whereas, it is preferred to use compound of formula X when Y=O and W=S.

The carbamates of formula II, IV, VI, VII may be prepared by reacting appropriate phenacyl alcohol or thiol of formula XV wherein all the symbols are as defined earlier and B represents $SR_2$, $SOR_2$, $S(O)(NH)R_2$, $S(O)(NR_1)R_2$ respectively, with an appropriate isocyanate or



XV

+ $R_3CNY$ ⟶ II or IV or VI or VII

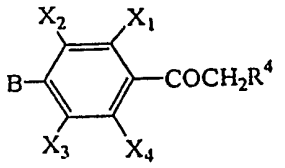
XVI

isothiocyanate of formula XVI where Y represent O or S respectively under appropriate conditions. The reactions may be carried out by heating a mixture of XV and XVI. Organic

solvent such as xylene or toluene or a mixture thereof may be used at a temperature range of 80 °C –200 °C.

The compound of formula IX where Y and W represents S may be obtained by the action of aniline $R^3NH_2$ with carbondisulfide in the presence of a base such as NaOH, KOH, $NH_3$, $Et_3N$, pyridine and the like. Solvents used may be alcohols such as methanol, ethanol, acetonitrile, THF, dioxane and the like. The compound of formula X, where W=S, may be obtained by reacting a thiourea of formula $R_3NHCSNR'R''$ wherein $R_3$ is as defined earlier and R', R'' may be same or different and represent H or a lower alkyl group, in an aqueous alcoholic medium in the presence of mineral acids such as HCl, $H_2SO_4$ or $H_3PO_4$.

The haloketones of formula VIII, XI, XII or XIII may be prepared by halogenation of corresponding ketones of formula XVII, where $X_1$, $X_2$, $X_3$, $X_4$, $R_4$ are as defined earlier and B represents $SR_2$, $SOR_2$, $S(O)(NH)R_2$, $S(O)(NR_1)NR_2$ respectively.

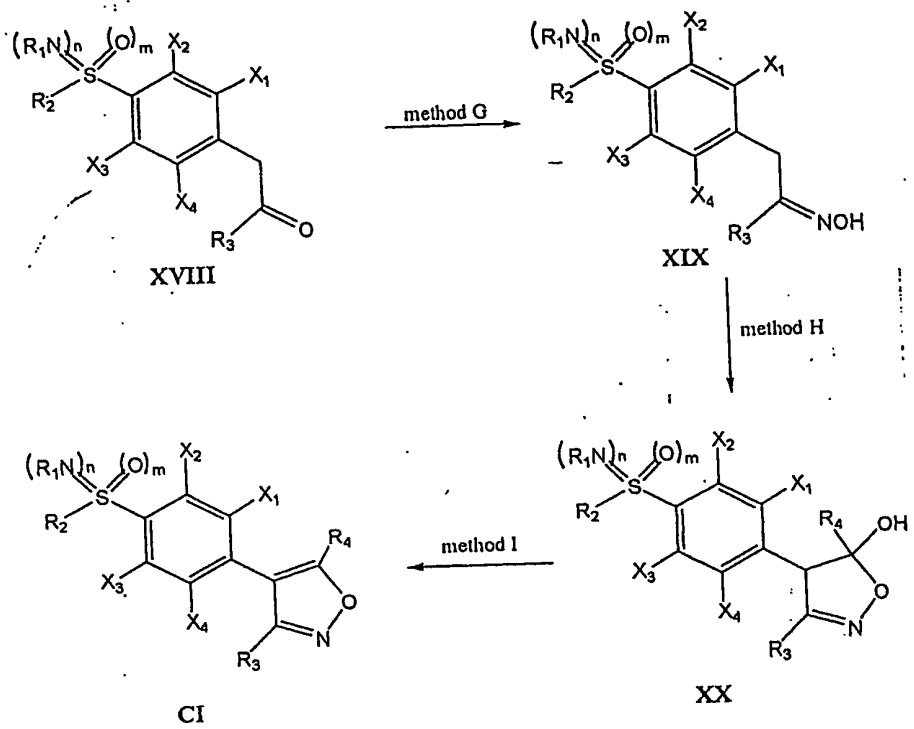



XVII

The halogenating agent may be chlorine, bromine, N-chlorosuccinimide, N-bromosuccinimide, perbromides like phenyltrimethylammonium tribromide and the like. Solvents such as acetic acid, $CH_2Cl_2$, $CHCl_3$, $CCl_4$, THF, alcohol may be used. Temperature in the range –20 °C to reflux temperature may be used.

The compounds of general formula (IB) may be prepared by one or more routes or combinations of reactions outlined in scheme 3 and scheme 4 which comprises:

SCHEME III

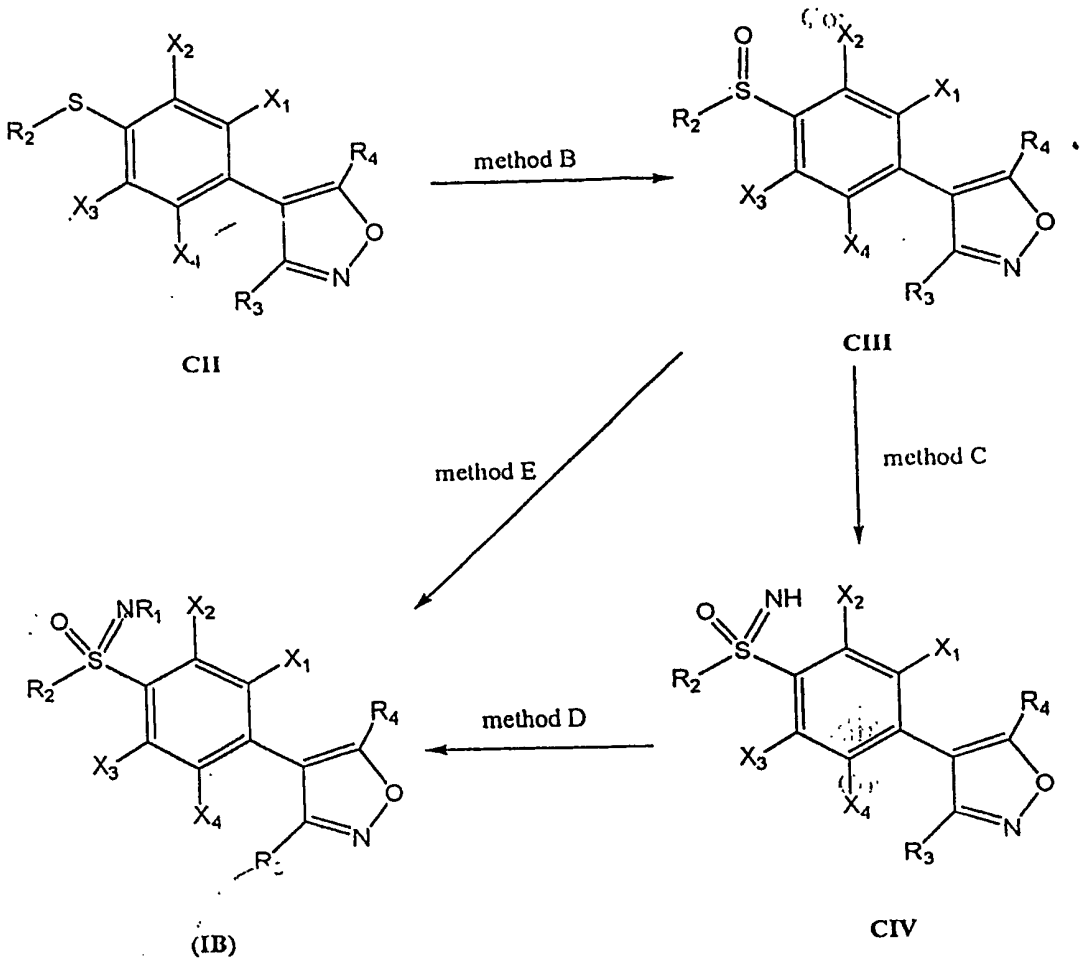



i) Reacting desoxybenzoin of general formula (XVIII) wherein all symbols are as defined earlier and n = 0 or 1 and m = 0 or 1 with hydroxylamine or its acid addition salt to get compound of general formula XIX wherein all symbols are as defined earlier;

ii) Reacting the compound of general formula XIX with atleast two equivalents of an appropriate base followed by treatment with an appropriate ester to afford an alcohol of general formula XX wherein all symbols are as defined earlier;

iii) heating the compound of general formula XX in an appropriate solvent in the presence of appropriate acid to get compound of general formula CI.

SCHEME IV




When n = 0 and m = 0, compound of formula XVIII represents compound of formula CII where all symbols are as defined earlier.

The compound of CII obtained as outlined in scheme III may be converted to compound of general formula (IB) defined earlier, by a method which comprises:

1) Oxidizing compound of formula CII with appropriate oxidizing agents to get a compound of general formula CIII where all the symbols are as defined earlier;
2) Reacting sulfoxide of formula CIII with appropriate agents to afford compound of general formula CIV where all the symbols are as defined earlier; Compound of formula CIV

represents compound of formula (IB) where R1 represents H and all other symbols are as defined earlier;

3) Optionally compound of formula CIV may be converted to compound of formula (IB) by suitable agents to get appropriate $R^1$ group. Alternatively, compound of formula CIII may be converted to compound of formula (IB) using appropriate agents.

4) Optionally, if desired, compound of formula CIV which represents compound of formula (IB) where $R^1$ represents H, or compound of formula (IB) are converted to pharmaceutically acceptable salts;

The reactions described in the processes outlined in the schemes III & IV above may be performed by using the methods described herein:

Method G:

The desoxybenzoin of formula XVIII may be converted to oxime XIX by reacting with hydroxyl amine or its acid addition salts. Reagents like sodium acetate may be used but not critical. Solvents such as alcohols like, ethanol, methanol, isopropanol and the like, THF, dioxane, toluene, xylene, cyclohexane, heptane, hexane, and the like or mixture thereof may be used. Temperature in the range 20 °C to reflux temperature of the solvent may be used, preferably in the range 60 °C to reflux temperature of the solvent(s) may be used. Inert atmosphere may be maintained using $N_2$, He, or argon gas.

Method H:

The oxime of formula XIX may be converted to alcohol of formula XX by reacting with two equivalents of a suitable base to produce a dianion which is further acylated. Bases such as n-BuLi, Sodium hydride, LDA, LiHMDS, NaHMDS and the like or a mixture thereof may be used. Temperature in the range of –78 °C to ambient temperature may be used. Preferably, the dianion formation is done at –78 ° to –40 °C range. Suitable acylating agents are esters, anhydrides, acyl imidazoles and the like. The reaction is conducted under a blanket of inert atmosphere using inert gases like $N_2$, He or Ar. Anhydrous condition is very critical for the reaction to give good product and yield.

Method I:

The alcohol of formula XX may be converted to isooxazole of formula CI by dehydration in the presence of an acid. Solvents such as ethanol, THF, toluene, xylene, and the like or a mixture thereof may be used. Suitable acids may be PTSA, $H_2SO_4$, HCl, HBr, camphorsulfonic acid, pyridinium paratoluene sulfonic acid and the like. The amount of acid used may be catalytic or substoichiometric or stoichiometric to effect the dehydration. Temperature in the range of ambient to reflux temperature of the solvent(s) may be used.

Method B:

The mercapto compound of formula CII may be converted to sulfoxide of formula CIII by reacting with an oxidizing agent as described in Method B earlier.

Method C:

The sulfoxide compounds of formula CIII may be converted to sulfoximine compounds of formula CIV by reacting with suitable iminating agents as described in Method C earlier.

Method D:

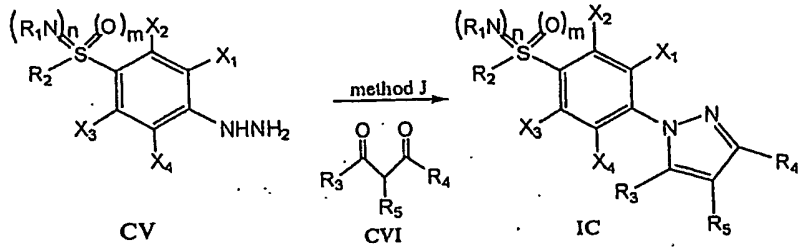
The sulfoximines of formula CIV may be converted to compounds of formula (IB) by reaction with appropriate alkylating/acylating agents in the presence of a base as described in method D earlier.

Method E:

The compounds CIII may be directly converted to compounds of formula (IB) by reacting with suitable reagents as described in Method E earlier, such as Tosyl azide, Chloramine T, in solvents such as ethanol, methanol and the like, followed by basification to yield $R_1$= Tosyl groups. Alternatively, reaction with aryl amines in the presence of t-BuOCl gives N-aryl sulfoximines.

The compound of general formula IC may be prepared by a process outlined in scheme V and scheme VI which comprises:

SCHEME V

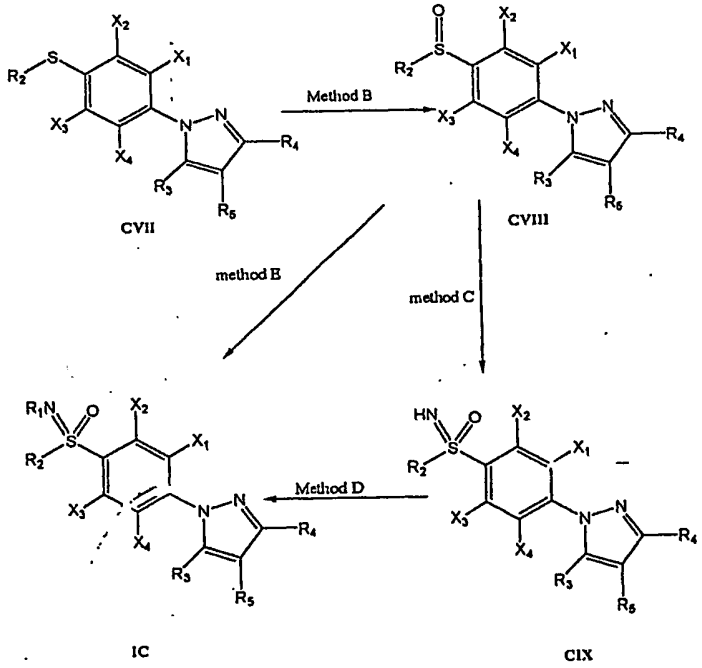



CV CVI IC

i) Reacting hydrazene of general formula (CV) wherein all symbols are as defined earlier and n = 0 or 1 and m = 0 or 1 with 1,3-diketone of general formula (CVI) to get compound of general formula (IC) wherein all symbols are as defined earlier;

ii)Optionally, compound of formula IC may be converted to pharmaceutically acceptable salts.

SCHEME VI




CVII CVIII IC CIX

When n = 0 and m = 0, compound of formula IC represents compound of formula CVII where all symbols are as defined earlier.

The compound of CVII obtained as in schemeVI may be converted to compound of general formula (IC) defined earlier, by a method which comprises:

i) Oxidizing compound of CVII with appropriate oxidizing agents to get a compound of general formula CVIII where all the symbols are as defined earlier;

ii) Reacting sulfoxide of formula CVIII with appropriate agents to afford compound of general formula IC where all the symbols are as defined earlier and R1 represents H.

iii) Optionally compound of formula IC obtained in ii) above may be converted to compound of formula (IC) by suitable agents to get appropriate $R^1$ group.

iv) Optionally, compound of formula CVIII may be directly converted to compound of formula IC using appropriate reagents.

v) Optionally, if desired, compound of formula (IC) may be converted to pharmaceutically acceptable salts;

The reactions described in the processes outlined in the schemes V & VI above may be performed by using the methods described herein:

Method J:

The hydrazene of formula CV or its acid addition salts may be converted to compound of formula (IC) by reacting with appropriately substituted 1, 3-diketones. Reagents like sodium acetate may be used but not critical. Solvents such as alcohols like, ethanol, methanol, isopropanol and the like, THF, dioxane, toluene, xylene, cyclohexane, heptane, hexane, and the like or mixture thereof may be used. Temperature in the range 20 °C to reflux temperature of the solvent may be used, preferably in the range 60 °C to reflux temperature of the solvent(s) may be used. Inert atmosphere may be maintained using $N_2$, He, or argon gas.

Method B:

The pyrazole compound of formula CVII may be converted to sulfoxide of formula CVIII by reacting with an oxidizing agent as described in method B earlier.

Method C:

The sulfoxide compounds of formula CVIII may be converted to sulfoximine compounds of formula (IC) by reacting with suitable iminating agents as described in method C earlier.

Method D:

The sulfoximines of (IC), where R1 represents H may be converted to compounds of formula (IC), where by reaction with appropriate alkylating/acylating agents in the presence of a base as described in method D earlier.

Method E:

The compounds CVIII may be directly converted to compounds of formula (IC) by reacting with suitable reagents; such as Tosyl azide, Chloramine T, in solvents such as ethanol, methanol and the like, followed by basification to yield $R_1$= Tosyl groups. Alternatively, reaction with aryl amines in the presence of t-BuOCl gives N-aryl sulfoximines.

Pharmaceutically acceptable salts forming part of this invention are intended to define but not limited to salts of the carboxylic acid moiety when present in the molecule such as alkali metal salts like Li, Na, and K salts; alkaline earth metal salts like Ca and Mg salts; salts of organic bases such as lysine, arginine, guanidine and its derivatives, which may be optionally substituted, diethanolamine, choline, tromethamine and the like; ammonium or substituted ammonium salts and aluminium salts. Salts may be acid addition salts which defines but not limited to sulfates, bisulfates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, fumarates, maleates, citrates, succinates, palmoates, methanesulfonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

It will be appreciated that in any of the above mentioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal in such protecting groups are those conventional methods appropriate to the molecule being protected. T. W. Greene and P. G. M. Wuts "Protective groups in Organic Synthesis", John Wiley & Sons, Inc, 1999, 3rd Ed., 201-245 along with references therein.

The pharmaceutically acceptable salts forming a part of this invention may be prepared by treating the compound of formula (I) with 1-6 equivalents of a base such as sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium tert-butoxide, calcium hydroxide, calcium acetate, calcium chloride, magnesium hydroxide, magnesium chloride, magnesium alkoxide and the like. Solvents such as water, acetone, ether, THF, methanol, ethanol, t-butanol, 2-butanone, dioxane, propanol, butanol, isopropanol, di*iso*propyl ether, *tert*-butyl ether or mixtures thereof may be used. Organic bases such as lysine, arginine, methyl benzylamine, ethanolamine, diethanolamine, tromethamine, choline, guanidine and their derivatives may be used. Acid addition salts, wherever applicable may be prepared by treatment with acids such as tartaric acid, mandelic acid, fumaric acid, malic acid, lactic acid, maleic acid, salicylic acid, citric acid, ascorbic acid, benzene sulfonic acid, p-toluene sulfonic acid, hydroxynaphthoic acid, methane sulfonic acid, acetic acid, benzoic acid, succinic acid, palmitic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and the like in solvents such as water, alcohols, ethers, ethyl acetate, dioxane, THF, acetonitrile, DMF or a lower alkyl ketone such as acetone, or mixtures thereof.

Another aspect of the present invention comprises a pharmaceutical composition, containing at least one of the compounds of the general formula (I), their derivatives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates thereof as an active ingredient, together with pharmaceutically employed carriers diluents and the like.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: the Science and

Practice of Pharmacy, 19th Ed., 1995. The compositions may be in the conventional forms, such as capsules, tablets, powders, solutions, suspensions, syrups, aerosols or topical applications. They may contain suitable solid or liquid carriers or in suitable sterile media to form injectable solutions or suspensions. The compositions may contain 0.5 to 20 %, preferably 0.5 to 10 % by weight of the active compound, the remaining being pharmaceutically acceptable carriers, excipients, diluents, solvents and the like.

Due to their low COX-1 activity, the compounds of formula (I) represent good anti-inflammatory compounds and have the benefit of significantly less harmful side effects than the NSAIDs commonly used (e.g. gastrointestinal toxicity), renal side effects, reduced effect on bleeding times and asthma induction in aspirin-sensitive subjects.

The present invention provides a compound of formula (I) for use in a method of treatment of the human or animal body by therapy, in particular for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention of colorectal cancer.

Another objective of the present invention is to provide for the use of compound of formula (I) in the manufacture of a medicament for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention of colorectal cancer.

The compounds of the present invention are useful in the treatment of inflammation and inflammation related disorders by administering the subject a therapeutic amount of the compound of formula-I or its active salt. Inflammation is associated with a variety of disease conditions. A list of such disease conditions which can be treated by cyclooxygenase inhibitors and COX-2 inhibitors in particular, are disclosed in US 5604,253 and 5908,852 and WO 9638442, 9603392 and WO 9714691. Such conditions includes pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhoea, headache, toothache, sprains and strains, menstrual cramps, premature labor, Such compounds may also be used in the treatment of arthritis, including but not limited to

rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. They may also be used in the treatment of skin inflammation disorders such as psoriasis, eczema, burning and dermatitis.

The compounds of formula (I) can also be used as alternative to conventional NSAIDs, particularly where such non-steroidal anti-inflammatory drugs may be contraindicated such as the treatment of patients with gastrointestinal disorders including peptide ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis Crohn's disease, inflammatory bowel syndrome and irritable bowl syndrome, ulcerative colitis, Crohn's disease, gastrointestinal bleeding and coagulation disorders, kidney disease (e.g. impaired renal function), those prior to surgery or taking anticoagulants, and those susceptible to NSAIDs.

In addition, compounds of the present invention may inhibit cellular neoplastic transformations and metastatic tumour growth and hence useful in the treatment of cancer. In particular, the present invention provides for a method for treating neoplasia that produces prostaglandin by treating the subject to a therapeutic amount of the compound (I). Thus the compounds of the present invention would be useful for the prevention and treatment of cancer, such as colorectal cancer and cancer of the lip, mouth, esophagus, breast, lung, prostate, bladder, pancreas, cervix and skin, small bowel cancer, stomach cancer ovary cancer, cervical cancer and the like. Use of COX-2 inhibitors in aforesaid diseases are discussed in US 5972,986 and WO 0076983 & 0114691. Such compounds will also be useful in the treatment of inflammation in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling after injury, myocardial ischemia and the like. The compounds would also be useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. They are also useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis.

The compounds of the present invention would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease (*Bratisl Lek Listy* 2001;102(3):123-132) and central nervous system damage resulting from stroke, ischemia and trauma. The compounds of the invention are useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects. These compounds would be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and atherosclerosis

The compounds of the present invention may also be useful in the treatment of angiogenesis-mediated disorders. Angiogenesis mediated disorders may be treated with cyclooxygenase inhibitors are described in U.S. 6025,353 and WO 0076983. According to these patents such disorders include, for example, metastasis, corneal graft rejection, ocular neovascularization, diabetic retinopathty, retrolental fibroplasia, neovascular glaucoma, gastric ulcer, infantilehemaginomas, angiofibroma of the nasopharynx, avascular necrosis of the bone and endometrosis.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals including mammals, rodents, and the like. More preferred animals include horses, dogs and cats.

The present compounds may also be used as co-therapies, partially or completely, in place of other conventional anti-inflammants like steroids, NSAIDs, 5-lipoxygenase inhibitors, $LTB_4$ receptor antagonists and $LTA_4$ hydrolase inhibitors. They can also be used in combination therapies with opoids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers among others.

The present invention also relates to a pharmaceutical composition for the treatment of a disorder or condition that can be treated by selectively inhibition COX-2 in a mammal, preferably a human, cat, livestock or dog, comprising a COX-2 selective inhibiting effective

amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention also relates to a method for treating a disorder or condition that can be treated or prevented by selectively inhibiting COX-2 in a mammal, preferably a human, cat, dog livestock, comprising administering to a mammal requiring such treatment a COX-2 selective inhibiting effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of or a pharmaceutical composition for the treatment of inflammation and similar diseases which comprises administering a compound of formula (I) of this invention or its salt to a mammal including a human, cat, livestock or dog. The said inhibitory compound is used in combination with one or more other therapeutically active agents such as:

A) In a condition where a joint has become inflamed along with a bacterial, fungal, protozoal, and/or viral infection, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal, and/or antiviral therapeutic agents.

   i) During multi-fold treatment of pain and inflammation is required, the compound should be administered in combination with inhibitors of other mediators of inflammation, consisting of members of the following groups: NSAIDS, $H_1$-receptor antagonists, kinin-$B_1$- and $B_2$ - receptor antagonists; prostaglandin inhibitors selected from the group consisting of PGD-, PGF-$PGI_2$-, and PGE-receptor antagonists; thromboxane $A_2$ ($TXA_2$-) inhibitors; 5-, 12- and 15-lipoxygenase inhibitors; leukotriene $LTC_4$-, $LTD_4/LTE_4$-, and $LTB_4$-inhbitors; PAF-receptor antagonists; anti-inflammatory glucocorticoids; anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone, and benzbromarone.

B) When treating older mammals with geriatric disorders, the said compound is administered in combination with members selected from any of the following groups: cognitive therapeutics, anti-hypertensives and other cardiovascular drugs selected from among diuretics, vasodilators, β - adrenergic receptor antagonists, ACE inhibitors alone or in combination with neutral endopeptidase inhibitors intending to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction

For the treatment of any of the above-mentioned diseases the compounds of formula (I) may be administered, for example, orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles.

The compounds of the present invention is useful in the treatment of inflammatory diseases caused by cytokines, specially, TNF-α, by either inhibiting the production or by inhibiting the TNF-α converting enzyme (TACE) or by inhibiting TNF-α itself.

In general, the dosage for humans will range preferentially from 0.01 mg to 100 mg per kg of body weight per day, although variations will occur, depending upon the weight, sex and condition of the subject being treated, the state of the disease being treated and the particular route of administration. However, the preferred dosage level should be in the range of from 0.1 mg to 10 mg per kg of body weight per day in single or divided dosage.

For non-human mammals e.g. dogs, cats, horses or other livestock the dosage should be from about 0.01 mg/g to about 20.0 mg/kg/day, and more preferably from about 0.5 mg/kg to about 8.0 mg/kg/day.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes as previously indicated, in single or multiple doses. More specifically, the novel compounds described in the invention can be administered in a wide variety of different dosage forms, i.e., they may be

combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, trochees, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. The carriers may include solid diluents or fillers, sterile aqueous media and various nontoxic organic solvents etc. Moreover, for oral consumption, the pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds as described in the invention are present in the compositions at concentration levels ranging from 5% to 60% by weight, preferably 10% to 50% by weight.

For oral administration, the tablets may be combined with various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dipotassium phosphate and glycine along with various disintegrants such as starch more preferably corn, potato or tapioca starch, alginic acid, sodium carbonate and certain complex sillicates; together with binders like polyvinylpyrrolidone, sucrose, gelatin and acacia, humectants such as for example, glycerol; solution retarding agents, such as, for example paraffin; absorption accelerators such as, for example, quartenary ammonium compounds; wetting agents like cetyl alcohol and glycerol monostearate; absorbents like kaolin and bentonite clay. Additionally, magnesium stearate, sodium lauryl sulfate, talc, calcium stearate, solid polyethylene glycols and mixtures thereof are often added as lubricating agents for tabletting purposes. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Similar type of solid compositions may also be employed as fillers and excipients in soft and hard gelatine capsules; preferred materials includes lactose, milk sugar or high molecular weight polyethylene glycols.

The active compounds can also be in micro-encapsulated form using one or more of the excipients noted above. The solid dosage forms of tablets, dragees, capsules, pills, and the granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings which are well known in the field of pharmaceutical formulation art. In such solid dosage forms the active compound may be admixed with atleast one inert

diluent such as sucrose, lactose and starch. They may also contain, additional substances for e.g. tableting lubricants and other substances like magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the formulation may also contain buffering agents. They may also be so formulated that they release the active ingredient(s) only or preferentially in a certain part of the intestinal tract, optionally in a delayed manner. The same may be achieved using embedded agents like, for example, polymeric substances and waxes.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. For such oral consumption it is desirable to combine the active ingredient with various sweetening or flavoring agents, coloring matter or dyes, if so desired. The diluents may be selected from water, ethanol, propylene glycol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, 1,3 butylene glycol, dimethyl formamide, oils for e.g. cottonseed, groundnut, corn, germ, olive, castor, sesame oils and the like, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and esters of fatty acids like sorbitan and various combination thereof. For mammals other than humans, the composition of the active substance are suitably modified.

For delayed-, sustained-, and/or controlled-release compositions dosage forms will include compositions which produce ≥ 80% inhibition of COX-2 isozyme activity and the plasma concentration of the said inhibitor should be at least 3 fold and preferably 5 fold, the COX-2 $IC_{50}$ for a minimum period of 4-8 hours; though preferably the period should be for at least 24 hours.

For parenteral administration, the solutions of the compound is prepared in either sesame or peanut oil or in aqueous propylene glycol. The aqueous solutions should be suitably buffered (preferably pH>8) if necessary, and the diluent should be first rendered isotonic. The aqueous solutions are suitable for intravenous injection purposes while the oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The aforesaid compositions can be readily prepared under sterile conditions following well known standard pharmaceutical techniques by persons skilled in the art.

The compounds of formula (I) may also be administered in the form of suppositories for rectal or vaginal administration of the active ingredient. These compositions can be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at room temperature (for example, 10 °C to 32 °C) but liquid at the rectal temperature and will melt in the rectum or vagina to release the active ingredient. Such materials are polyethylene glycols, cocoa butter, suppository and wax.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

For transdermal and topical administration, the dosage forms will include ointments, pastes, creams, lotions, gels, powders, solutions, sprays and inhalants. Transdermal patches may be prepared following standard drug delivery techniques and applied to the skin of a mammal, preferably a human or a dog, to be treated. Ophthalmic solutions, ear drops, eye ointments, powders can also be used as a medium of providing therapeutic dosages to the patients as will be necessary.

The ointments, pastes, creams and gels may, in addition to the active ingredient, contain excipients like animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, zinc oxide or their mixtures.

Powders and sprays may contain, in addition to the active substance, excipients like lactose, talc, silicic acid, aluminium hydroxide, calcium silicates and polyamide powder, or their mixtures. Sprays will additionally contain propellants like chlorofluorohydrocarbons.

The compounds of the present invention have been tested for their biological activities by carrageenan foot pad edema test in male as well as female Wistar rats according to standard protocol described in literature (Winter *et. al*, *Proc. Soc. Exp. Biol. Med.*, **111**, 544, (1962) ; Otterness and Bliven, Laboratory Models for Testing NSAIDS, in Non-Steroidal Anti-inflammatory Drugs, ( J. Lombardino, ed.1985)). The compounds of the present invention

inhibited 20 % - 60 % rat paw edema at a dose of 30 mg/kg. The compounds of the present invention possess analgesic property and inhibited COX– 2 enzyme selectively.

Dated this 4th day of APRIL 2007

Signature

To
The Controller of Patents
The Patent Office,
at

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